Etiology & Pathogenesis of AKI

By

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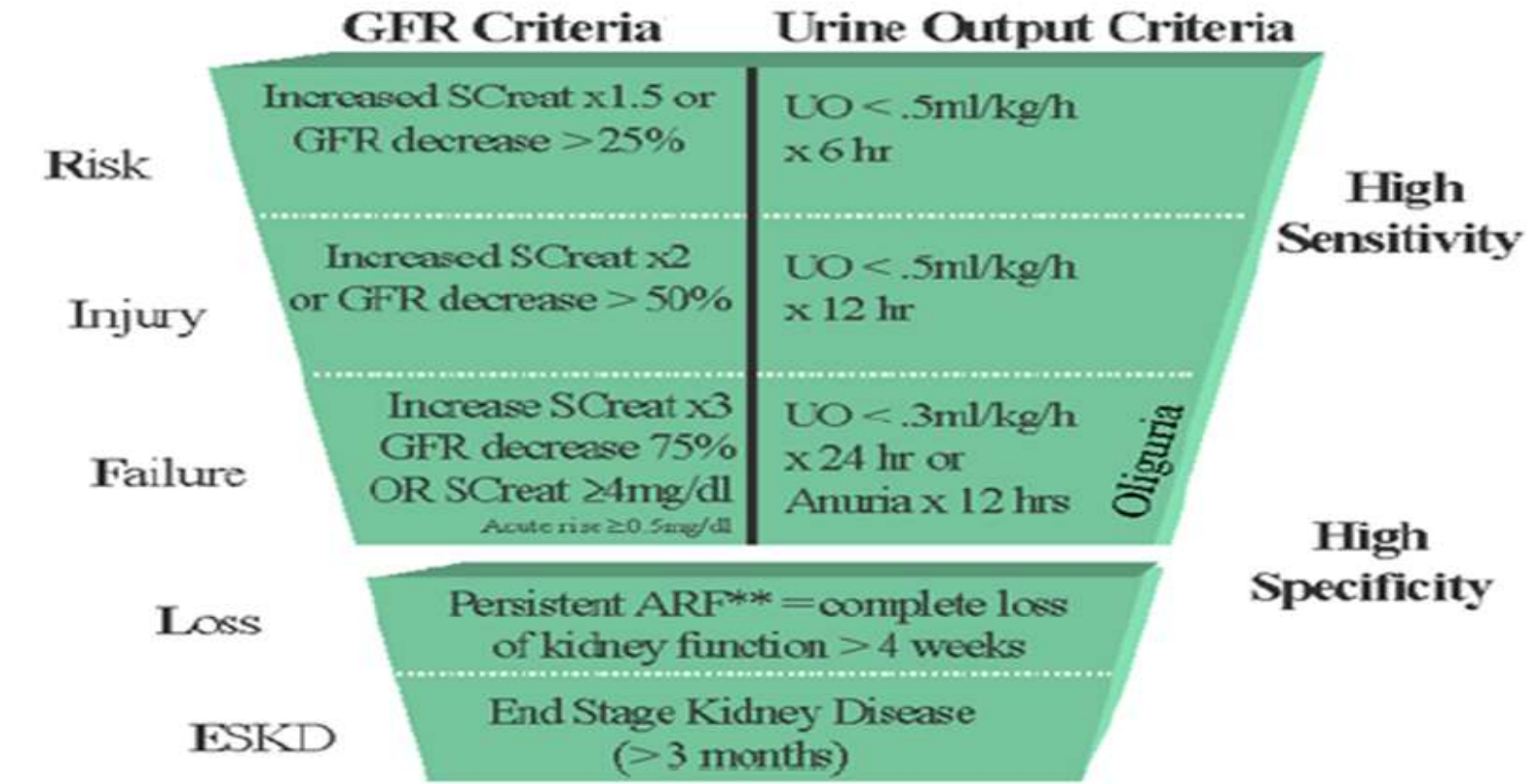
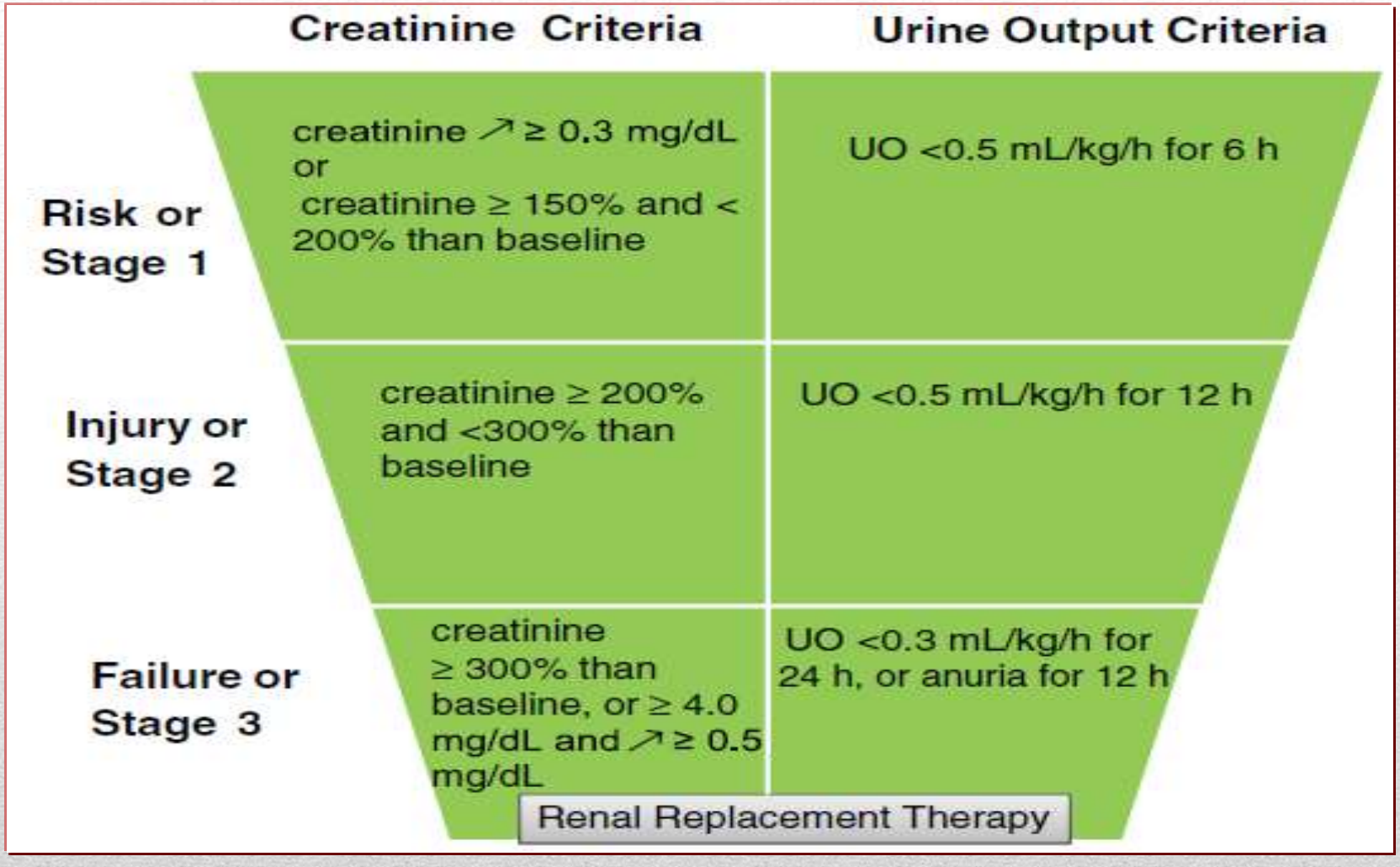
Definition

Abrupt decline in GFR sufficient to decrease the elimination of nitrogenous waste products (urea and creatinine) and other uremic toxins

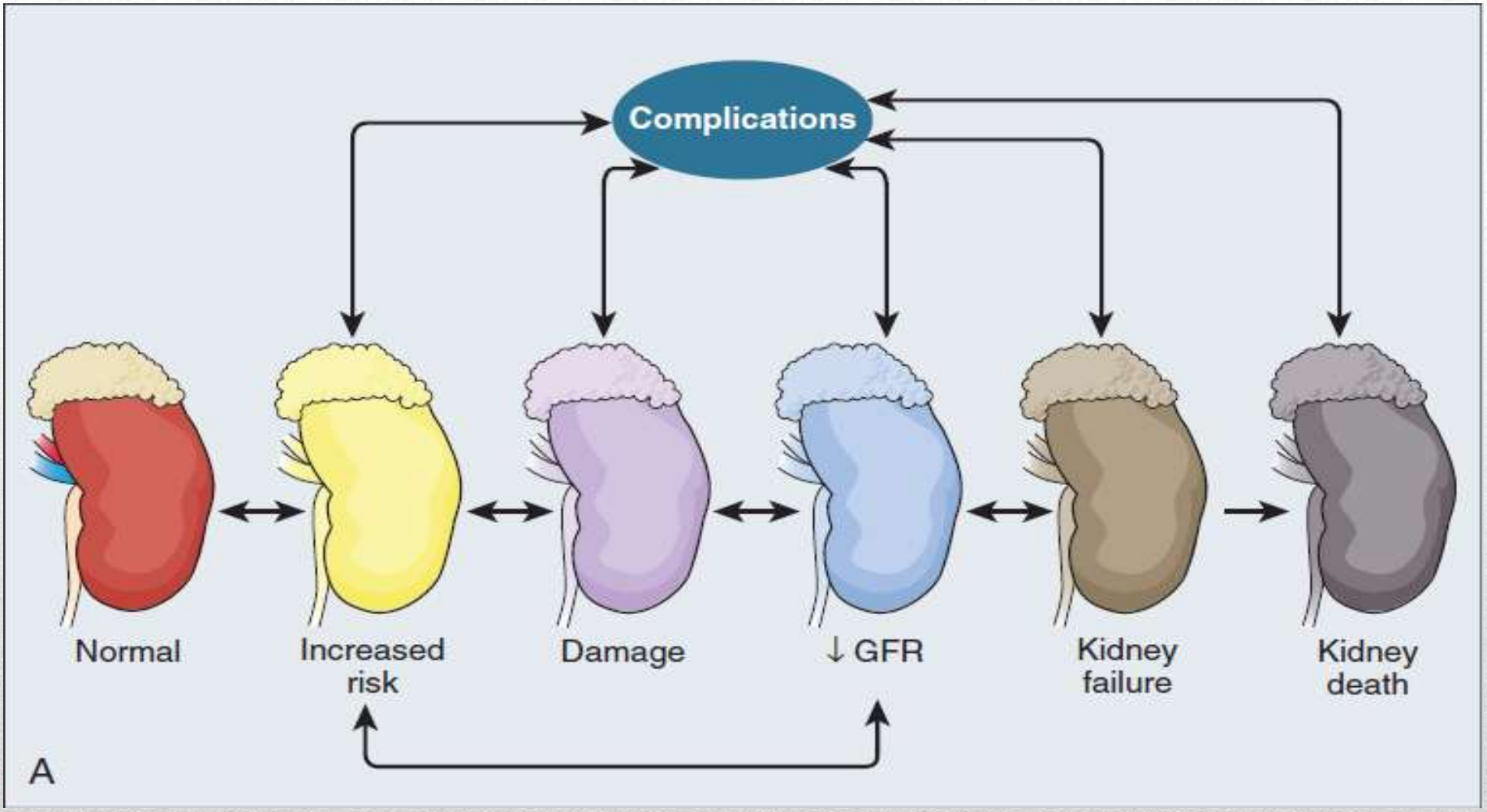


Proposed classification scheme for acute renal failure (ARF)

RIFLE Classification



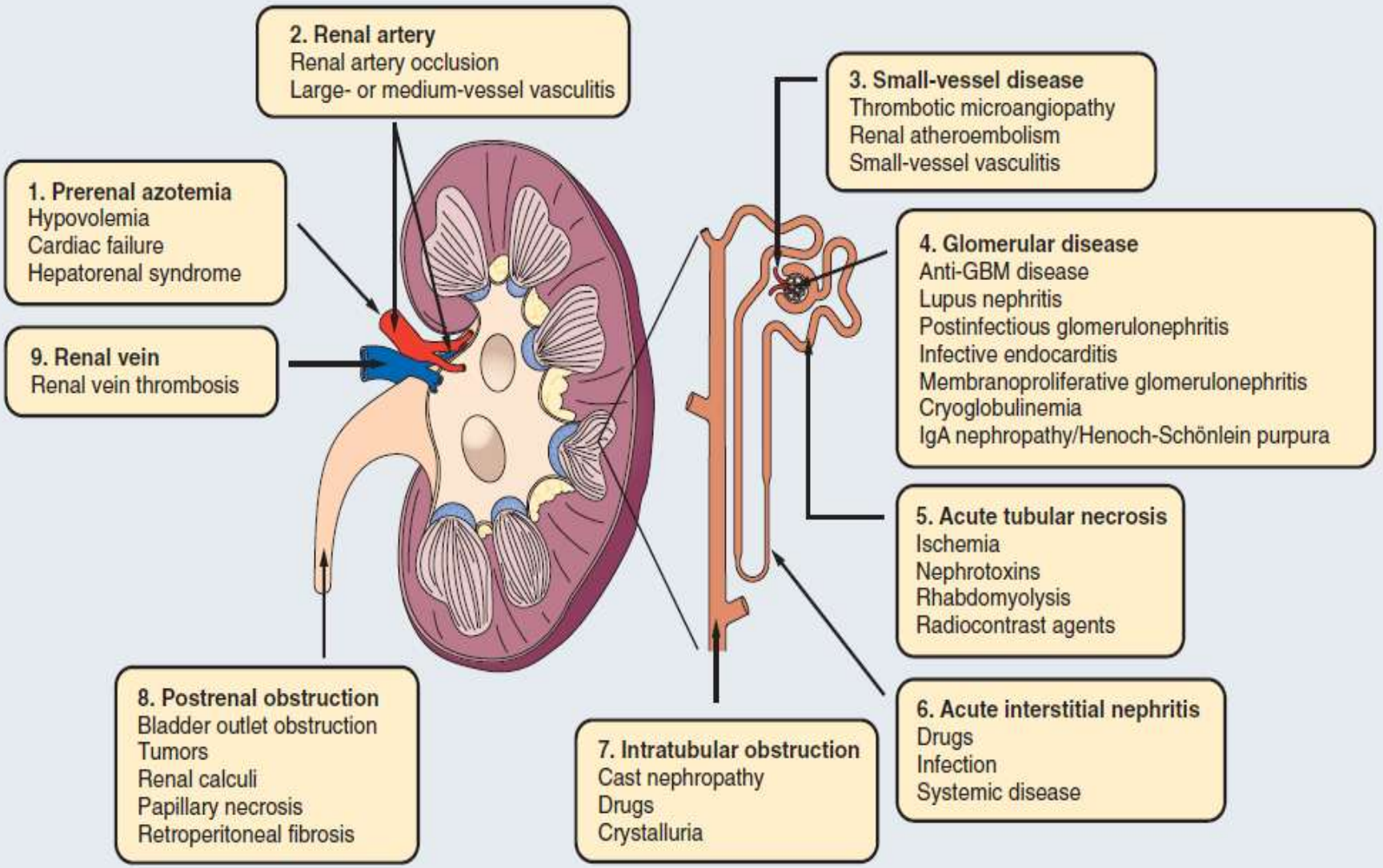
AKIN Classification



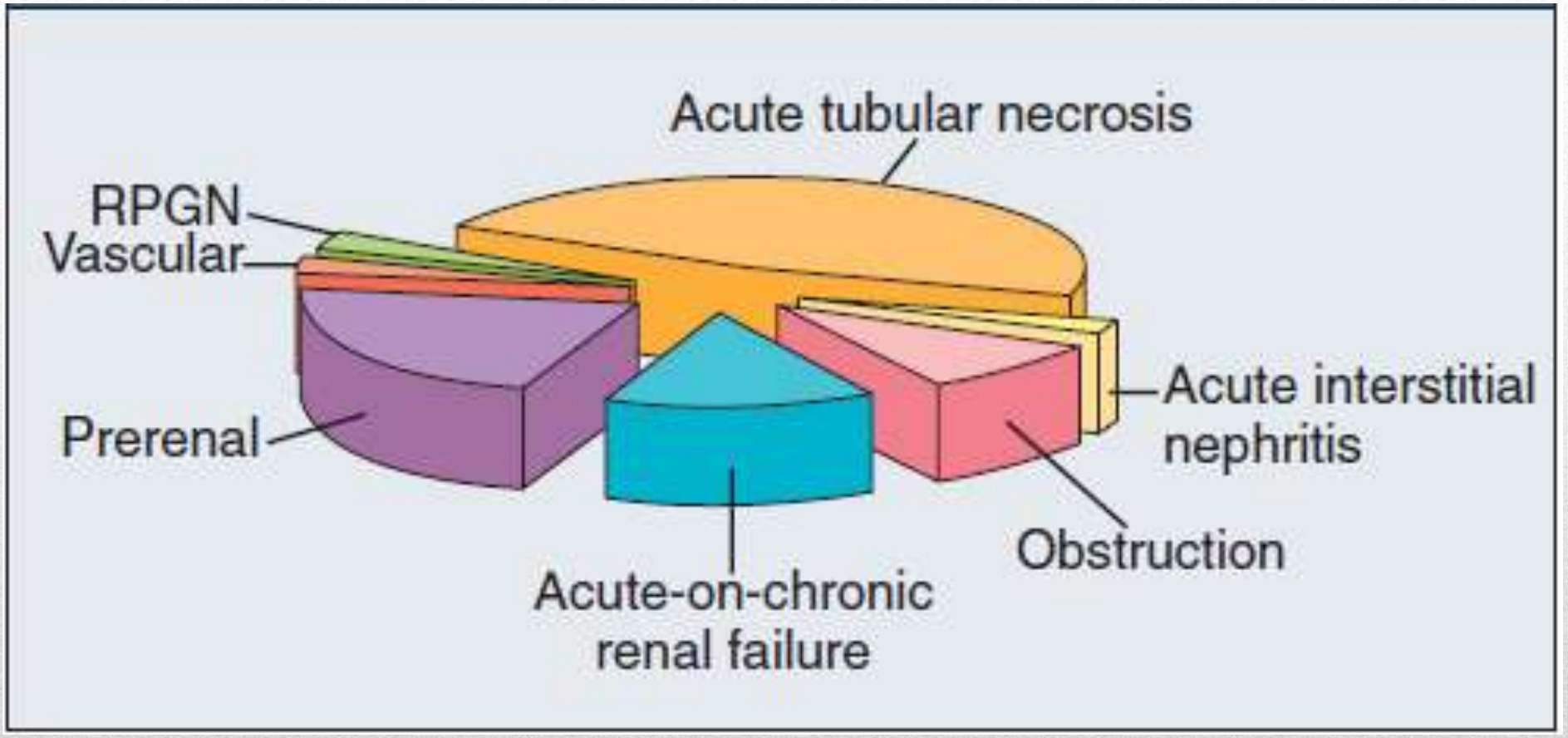
Kidney Injuiry Continuum

Patient Factors	Medications and Agents	Procedures
Pre-existing renal dysfunction	Nonsteroidal anti-inflammatory drugs	Cardiopulmonary bypass procedures
Sepsis		Surgery involving aortic clamp
Old age (>75)	Cyclooxgenase-2 inhibitors	Increased intra-abdominal pressure
Diabetes	Cyclosporine or tacrolimus	Large arterial catheter placement with risk for atheroembolization
Hepatic failure	Angiotensin-converting enzyme inhibitors	Liver transplantation
Atherosclerosis	Angiotensin receptor blockers	Kidney transplantation
Chronic hypertension		
Perioperative cardiac dysfunction	Use of venous or arterial radiocontrast agents	
Hypercalcemia		
Renal artery stenosis		

Major risk factors for AKI


2. Renal artery
Renal artery occlusion
Large- or medium-vessel vasculitis
3. Small-vessel disease
Thrombotic microangiopathy
Renal atheroembolism
Small-vessel vasculitis
1. Prerenal azotemia
Hypovolemia
Cardiac failure
Hepatorenal syndrome
4. Glomerular disease
Anti-GBM disease
Lupus nephritis
Postinfectious glomerulonephritis
Infective endocarditis
Membranoproliferative glomerulonephritis
Cryoglobulinemia
IgA nephropathy/Henoch-Schönlein purpura
9. Renal vein
Renal vein thrombosis
5. Acute tubular necrosis
Ischemia
Nephrotoxins
Rhabdomyolysis
Radiocontrast agents
8. Postrenal obstruction
Bladder outlet obstruction
Tumors
Renal calculi
Papillary necrosis
Retroperitoneal fibrosis
7. Intratubular obstruction
Cast nephropathy
Drugs
Crystalluria
6. Acute interstitial nephritis
Drugs
Infection
Systemic disease

Etiology



Causes of AKI in Hospital

Prerenal AKI

ECF volume depletion

- GIT losses: diarrhea, vomiting, prolonged nasogastric drainage
- Renal losses: diuretics, osmotic diuresis in hyperglycemia
- Dermal losses: burns, extensive sweating
- Third space loss: acute pancreatitis, muscle trauma

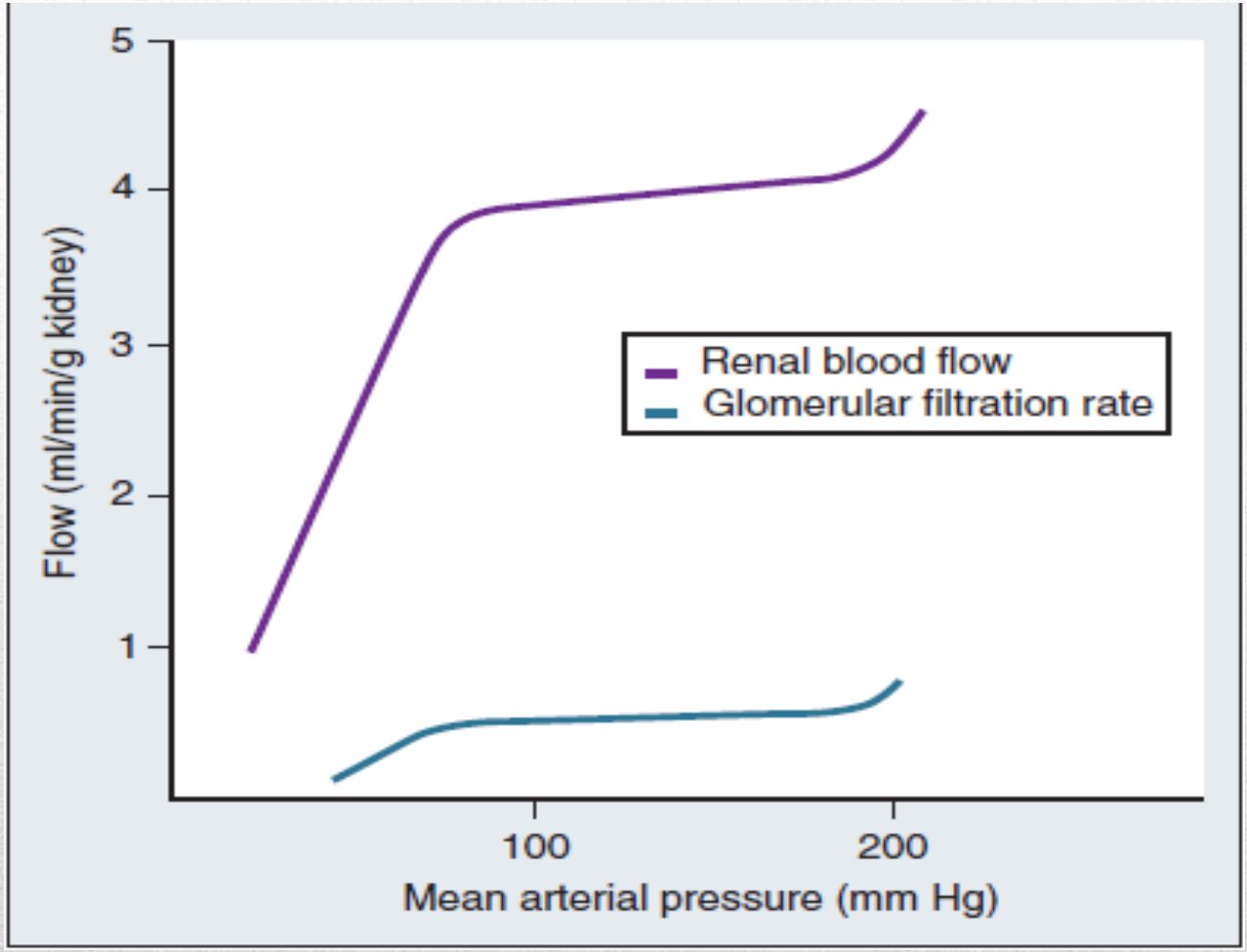
Prerenal AKI

Normal or increased ECF fluid

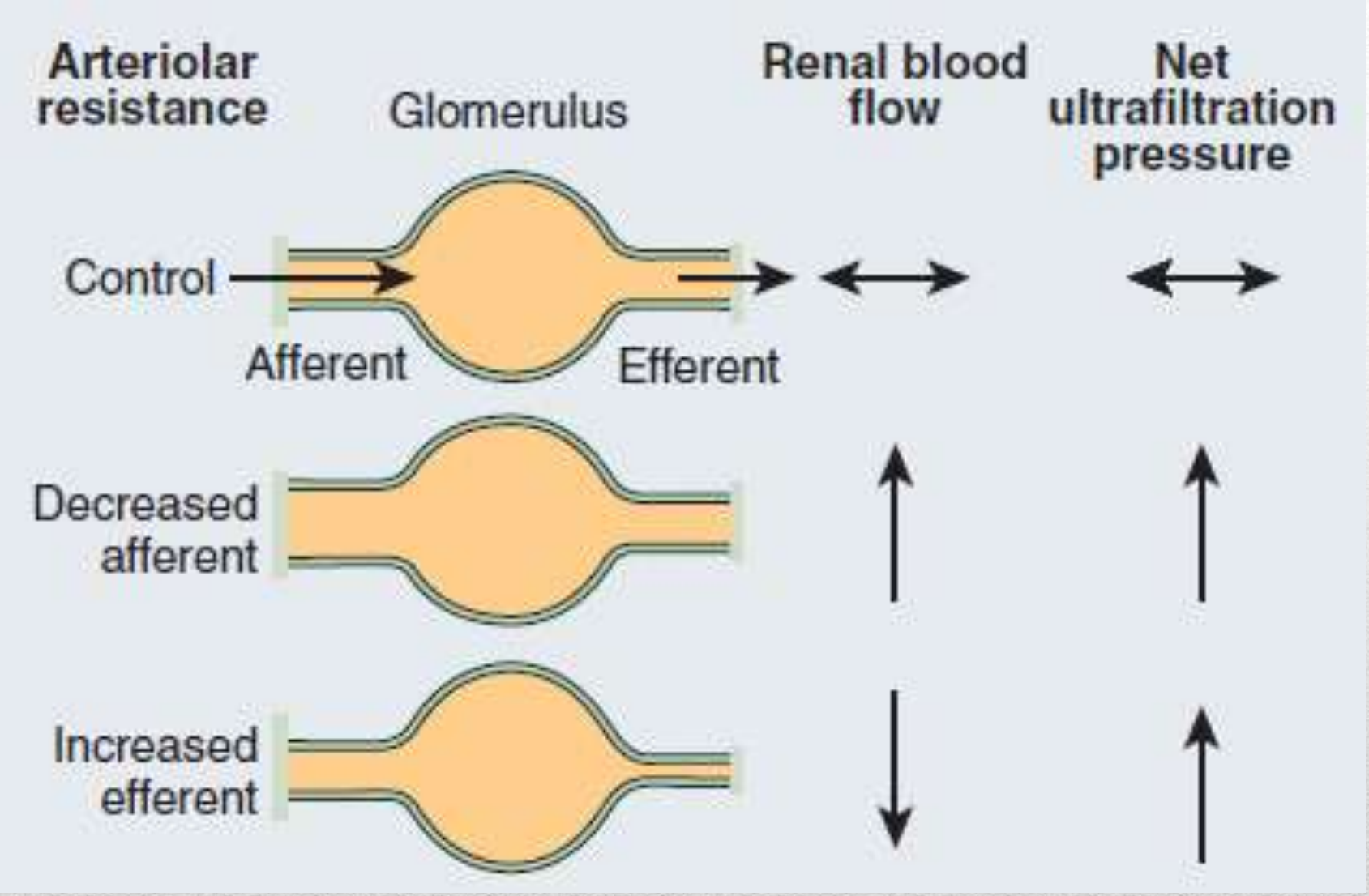
- Decreased COP: heart failure
- Systemic VD with redistribution of COP to extrarenal vascular beds: sepsis, liver cirrhosis.

Hyperoncotic state

- Mannitol, dextran and protein



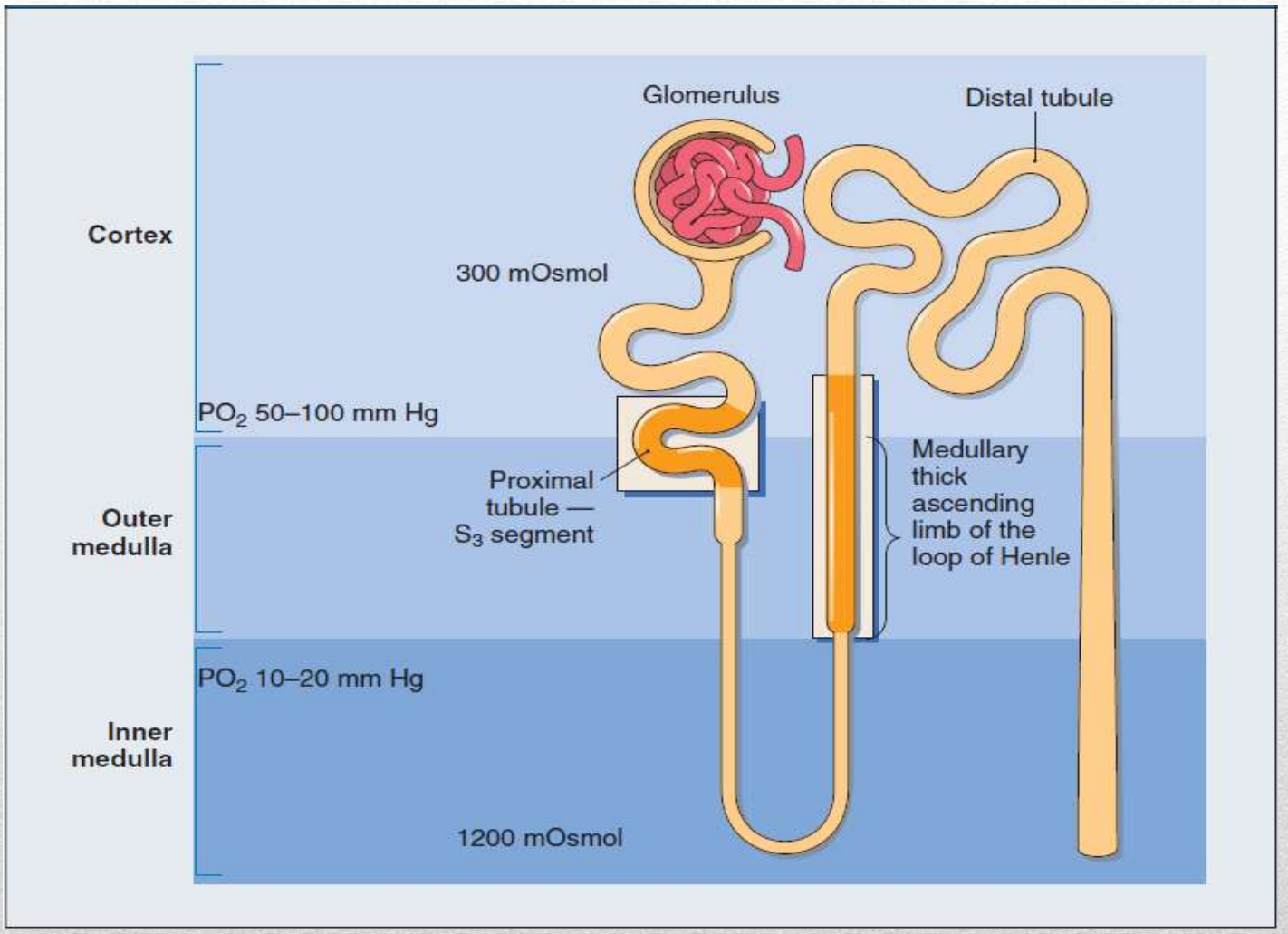
Pathophysiology of prerenal AKI


Arteriolar resistance
Glomerulus
Renal blood flow
Net ultrafiltration pressure
Control
Afferent
Efferent
Decreased afferent
Increased efferent

	Afferent Arteriolar Resistance	Efferent Arteriolar Resistance	Renal Blood Flow	Net Ultrafiltration Pressure	K_f	GFR
Renal sympathetic nerves	↑↑	↑	↓	↓	↓	↓
Epinephrine	↑	↑	↓	→	?	↓
Adenosine	↑	→	↓	↓	?	↓
Cyclosporine	↑	→	↓	↓	?	↓
NSAIDs	↑↑	↑	↓	↓	?	↓
Angiotensin II	↑	↑↑	↓	↑	↓	↓→
Endothelin 1	↑	↑↑	↓	↑	↓	↓
High-protein diet	↓	→	↑	↑	→	↑
Nitric oxide	↓	↓	↑	?	↑	↑(?)
Atrial natriuretic peptide (high dose)	↓	→	↑	↑	↑	↑
Prostaglandins E_2/I_2	↓	↓(?)	↑	↑	?	↑
Calcium channel blockers	↓	→	↑	↑	?	↑
ACE inhibitors/angiotensin receptor blockers	↓	↓↓	↑	↓	↑	?*

ATN

- Ischemic
- Toxic:
  - Endogenous: hemoglobinuria and myoglobinuria
  - Exogenous: aminoglycosides and radiocontrast agents

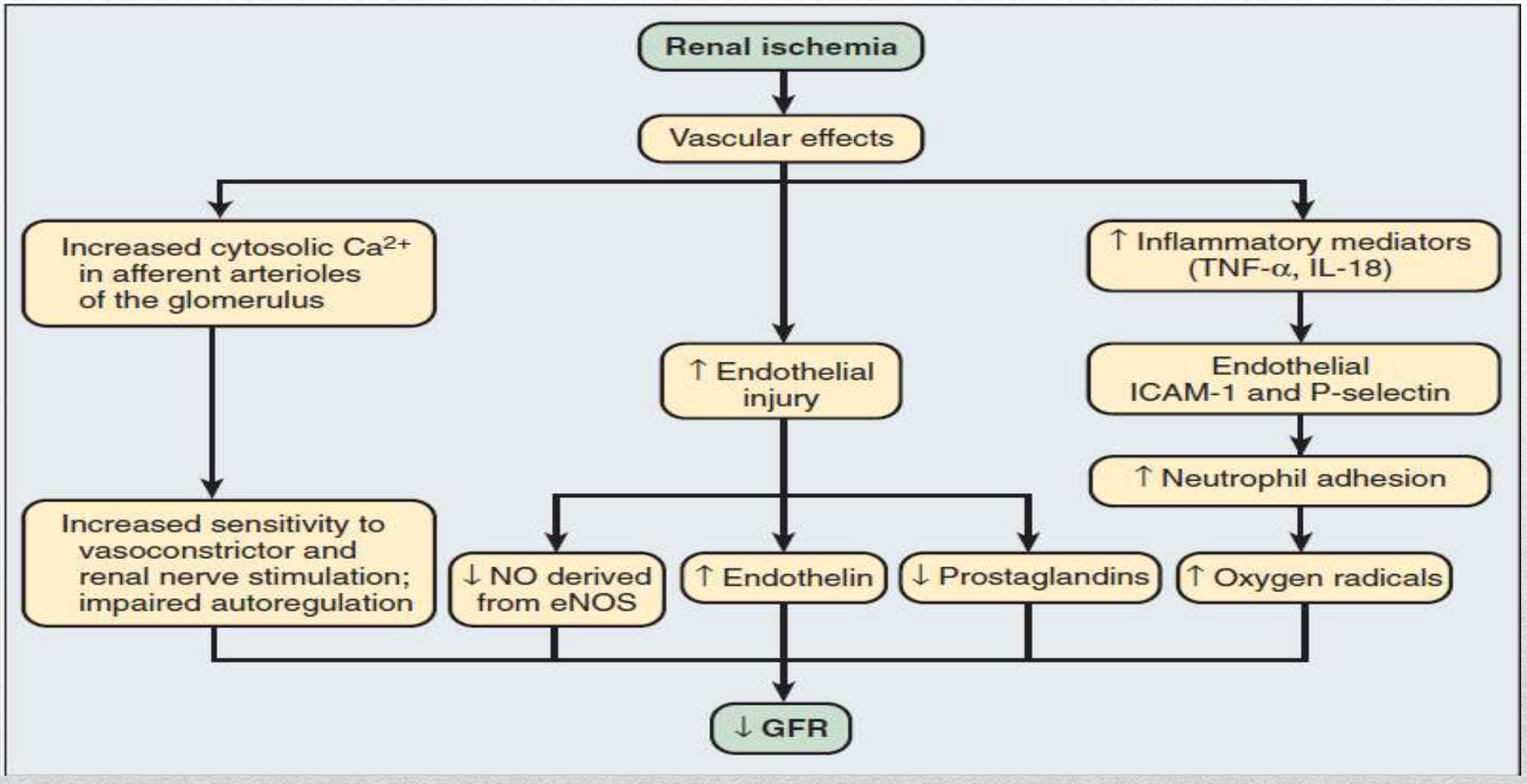


Pathophysiology of ATN

Pathophysiology of ATN

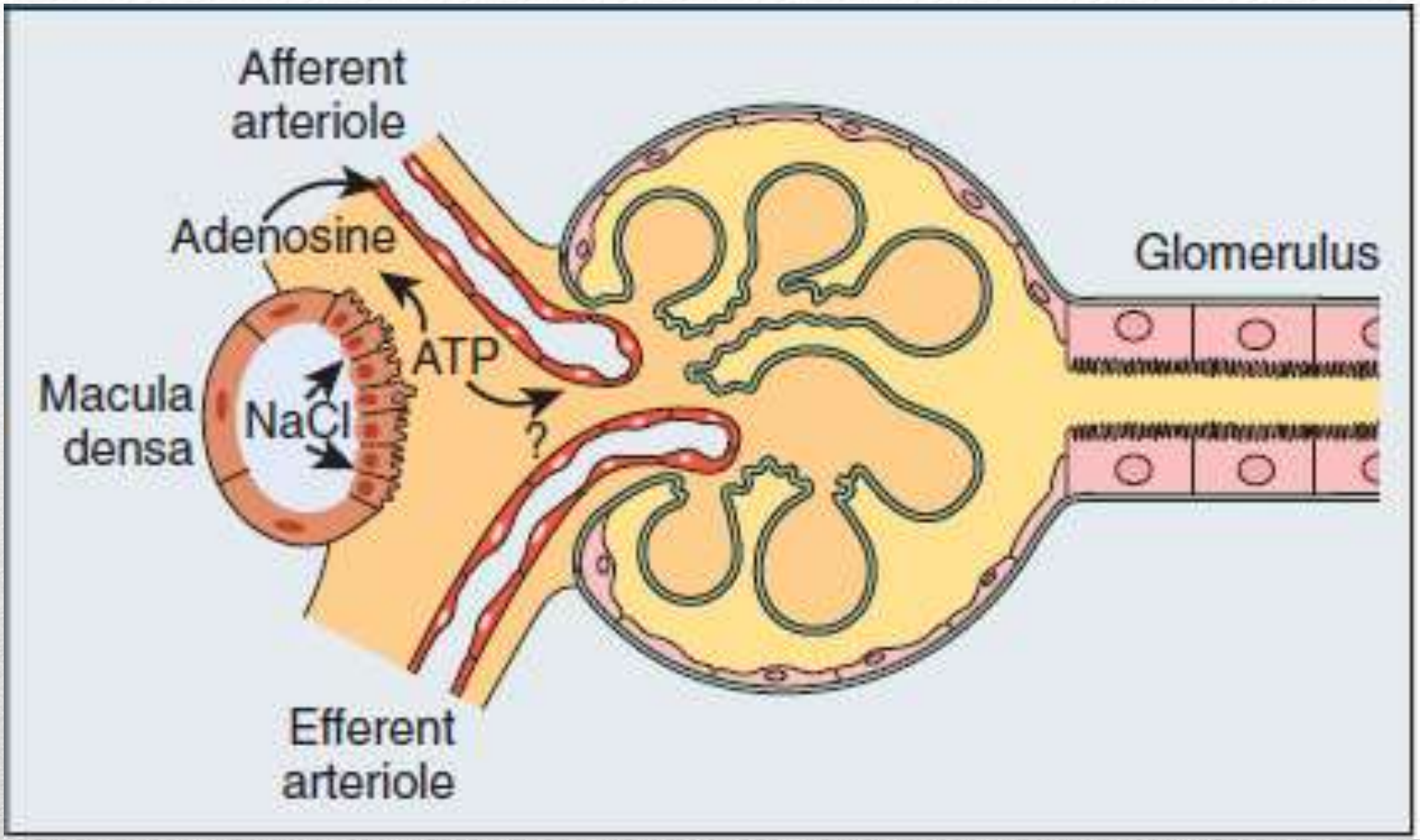
1. Impaired Renal Autoregulation

2. Intrarenal vasoconstriction



Pathophysiology of ATN

3. Tubuloglomerular feedback

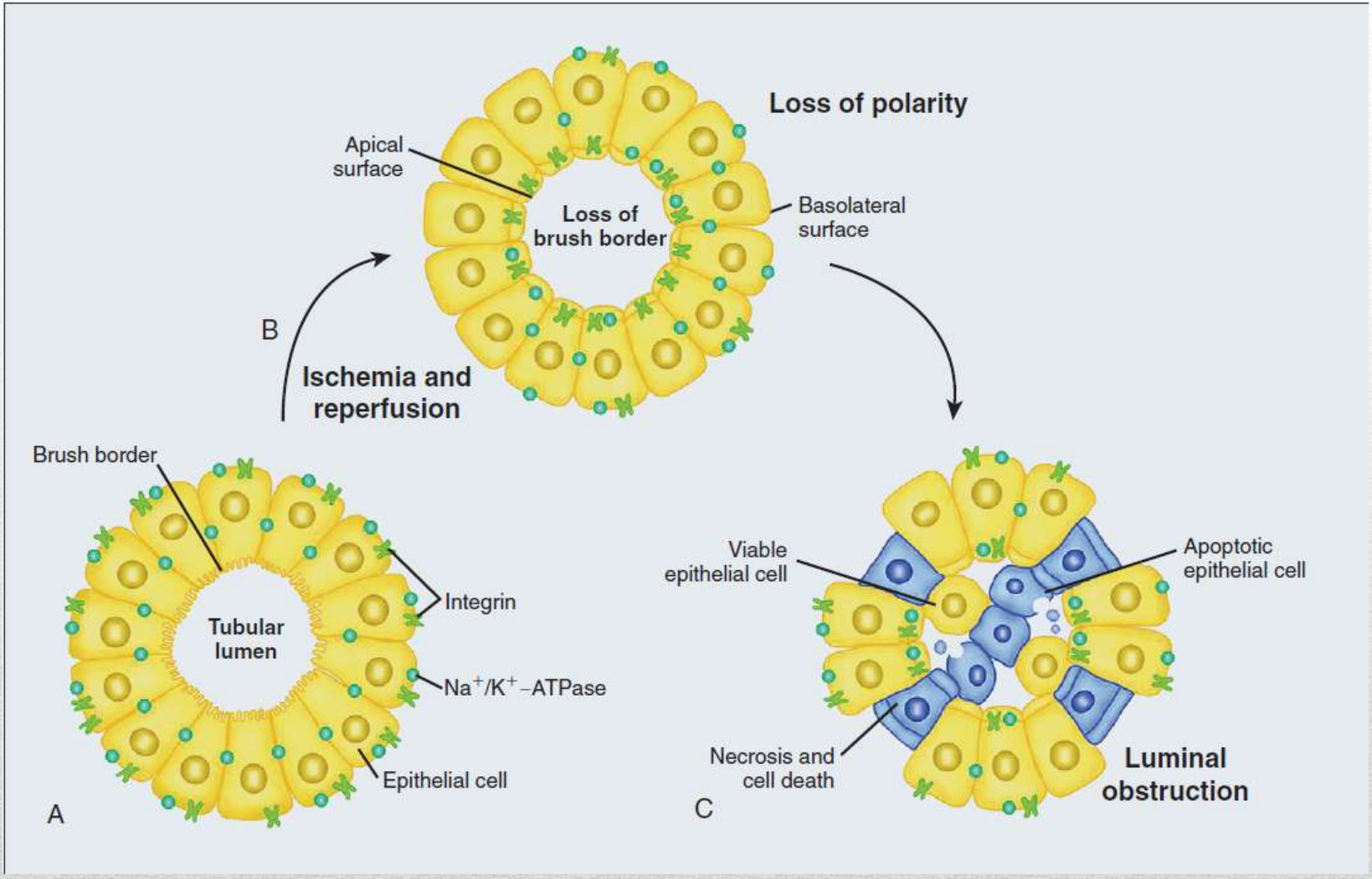


Pathophysiology of ATN

4. Inflammatory factors

- Proinflammatory cytokines: TNF-α, IL-6 and IL-1b
- Chemokines: MCP-1, IL-8, RANTES
- Innate immune systems: complement system and TLR2 and TLR4.
- Activation of complement
- T lymphocytes

Pathophysiology of ATN



Pathophysiology of ATN

Postrenal AKI

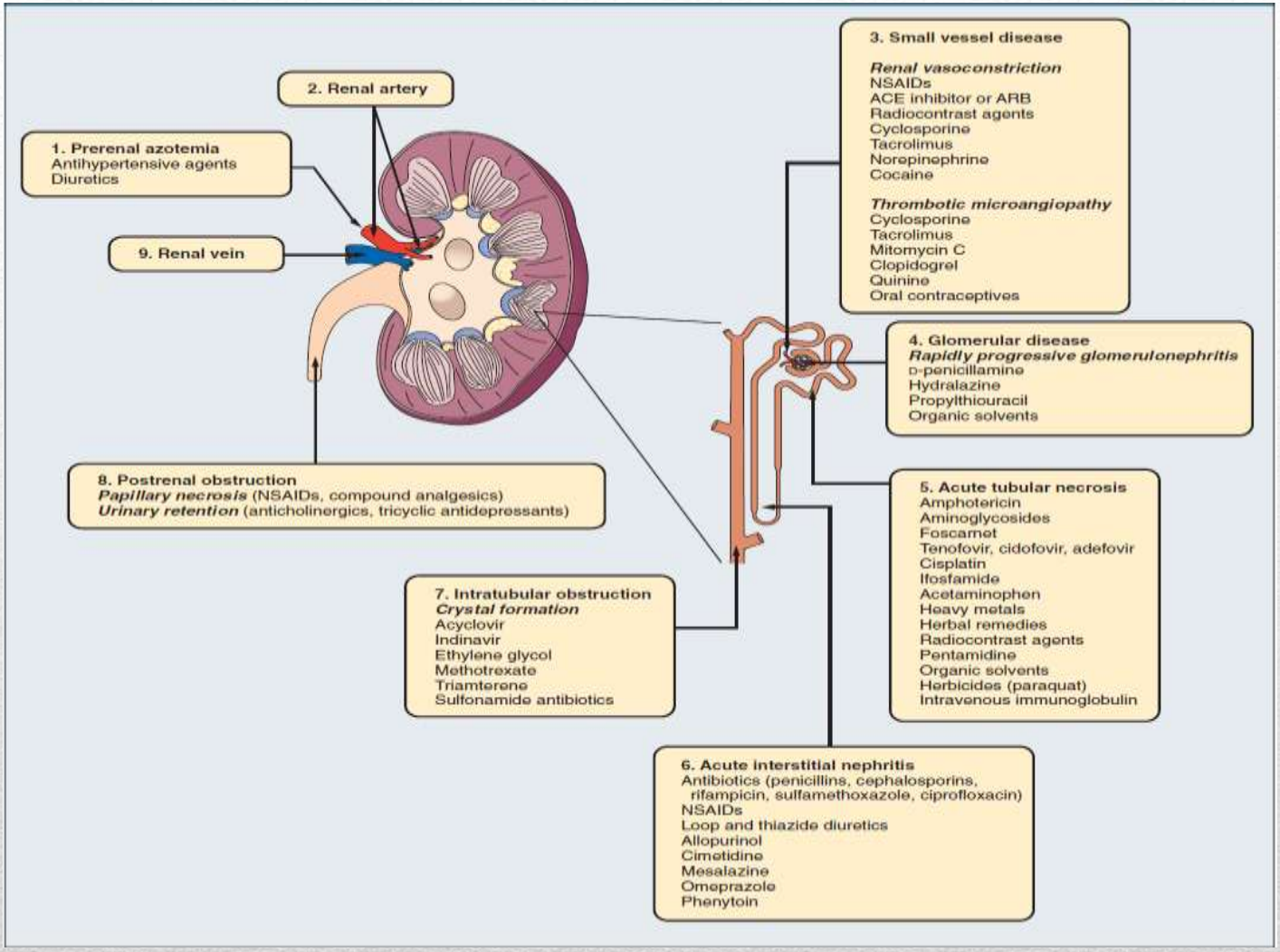
Intrarenal (tubular)

- Insoluble crystals (phosphate, methotrexate, acyclovir, sulfonamides, indinavir, uric acid, triamterene, oxalic acid)
- Protein (hemoglobin, myoglobin, paraprotein)

Extrarenal

- Obstruction of renal pelvis, ureters, bladder, or urethra

Specific Categories of AKI



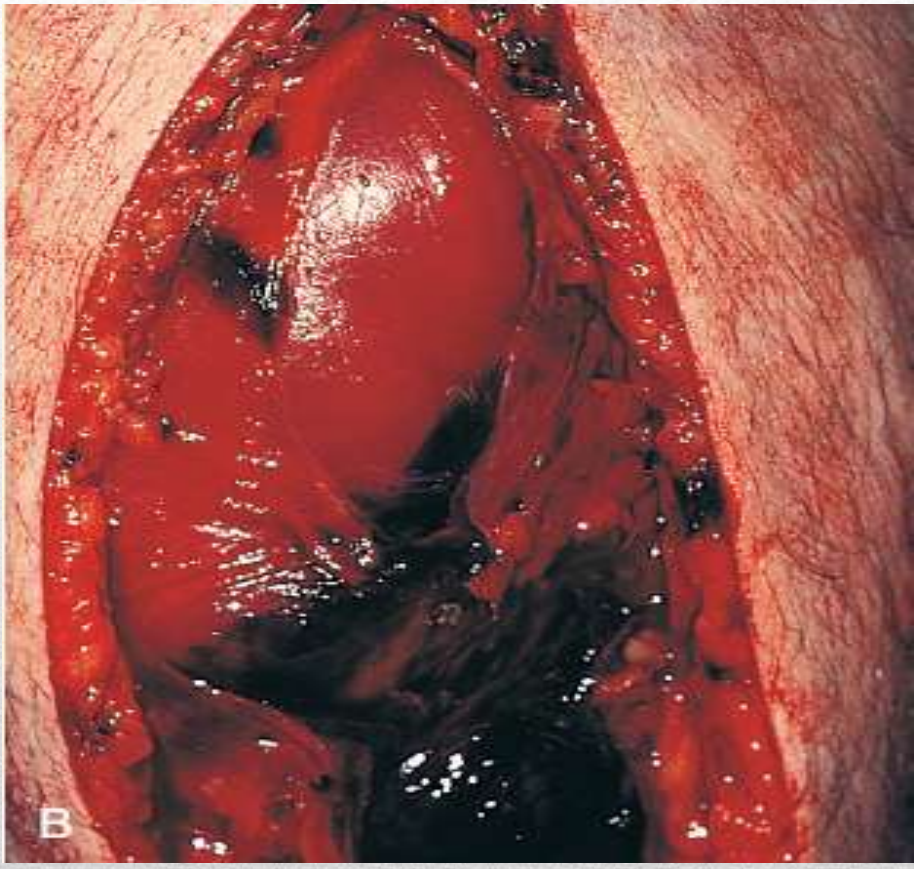
Nephrotoxic agents & AKI

1. Rhabdomyolysis

Muscle injury/ischemia	Trauma, pressure necrosis, electric shock, burns, acute vascular disease
Myofiber exhaustion	Seizures, excessive exercise, heat exhaustion
Toxins	Alcohol, cocaine, heroin, amphetamines, ecstasy, phencyclidine, snakebite
Drugs	Statins, fibrates, zidovudine, neuroleptic malignant syndrome, azathioprine, theophylline, lithium, diuretics
Electrolyte disorders	Hypophosphatemia, hypokalemia, excess water shifts (hyperosmolality)
Infections	Viral (influenza, HIV, Coxsackievirus, Epstein-Barr virus), bacterial (*Legionella*, *Francisella*, *Streptococcus pneumoniae*, *Salmonella*, *Staphylococcus aureus*)
Familial	McArdle's disease, carnitine palmitoyl transferase deficiency, malignant hyperthermia
Other	Hypothyroidism, polymyositis, dermatomyositis

Heme Pigment Nephropathy

Compartment Syndrome

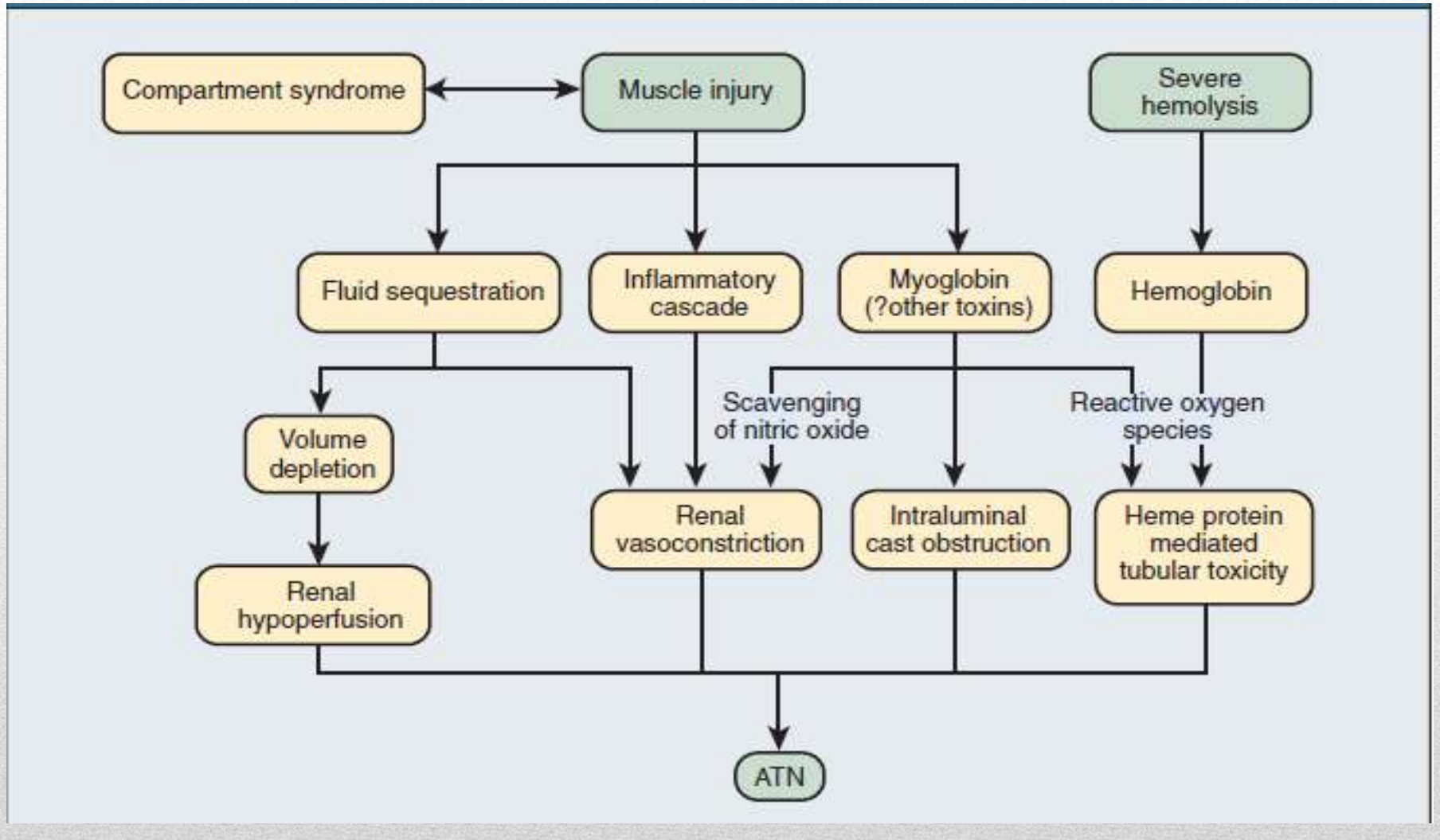


Heme Pigment Nephropathy

2. Hemoglobinuria

- Incompatible blood transfusion
- Autoimmune hemolytic anemia
- Malaria (blackwater fever),
- Glucose-6-phosphate dehydrogenase deficiency
- Paroxysmal nocturnal hemoglobinuria
- March hemoglobinuria
- Toxins: dapsone, venoms

Heme Pigment Nephropathy



Pathophysiology of Heme Pigment Nephropathy

Risk factors

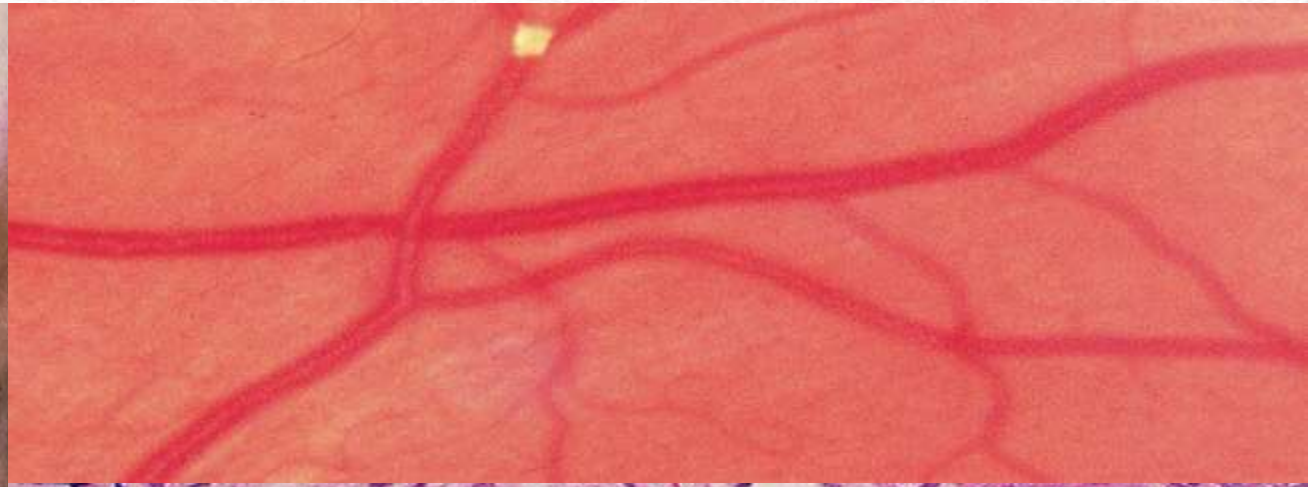
- Creat. > 1.5 mg/dl
- Systolic BP < 80 mmHg for > 1 hr or need for inotropic support
- Use of IABP
- Heart failure (NYHA class 3 or 4)
- History of pulmonary edema
- Volume of contrast > 100 ml

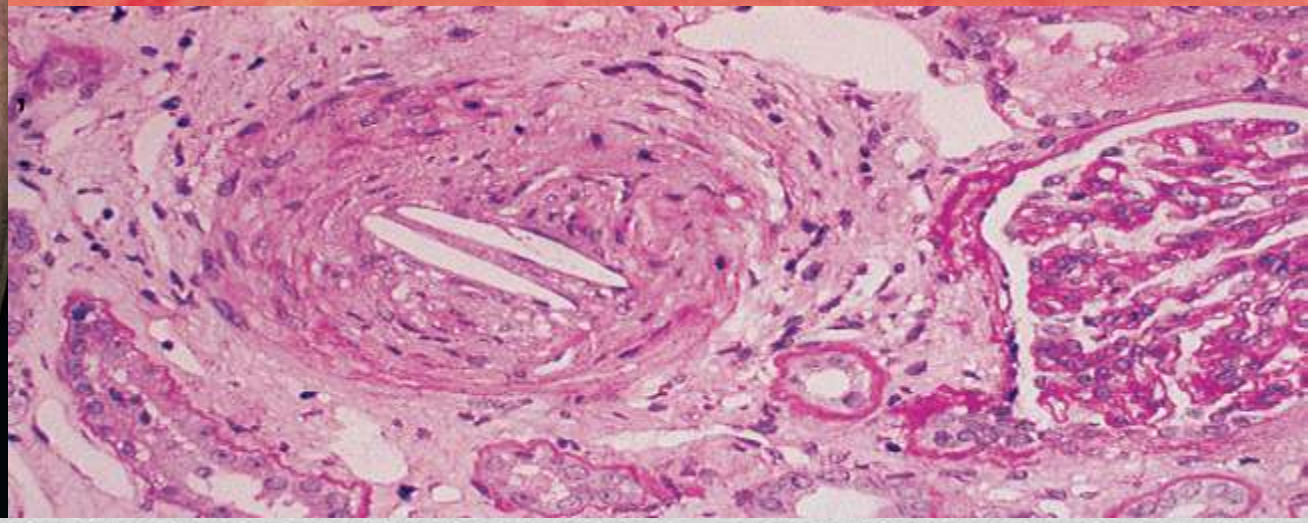
Contrast nephropathy

- Age > 75 years
- DM
- Anemia, blood loss
- High osmolar contrast agent
- Volume depletion
- Concurrent nephrotoxic agents: NSAIDs or ACE inhibitors.+

Pathogenesis

- Medullary hypoxia: renal VC
- Direct tubular epithelial cell toxicity: ROS





Atheroembolic renal disease

The Thrombotic microangiopathies

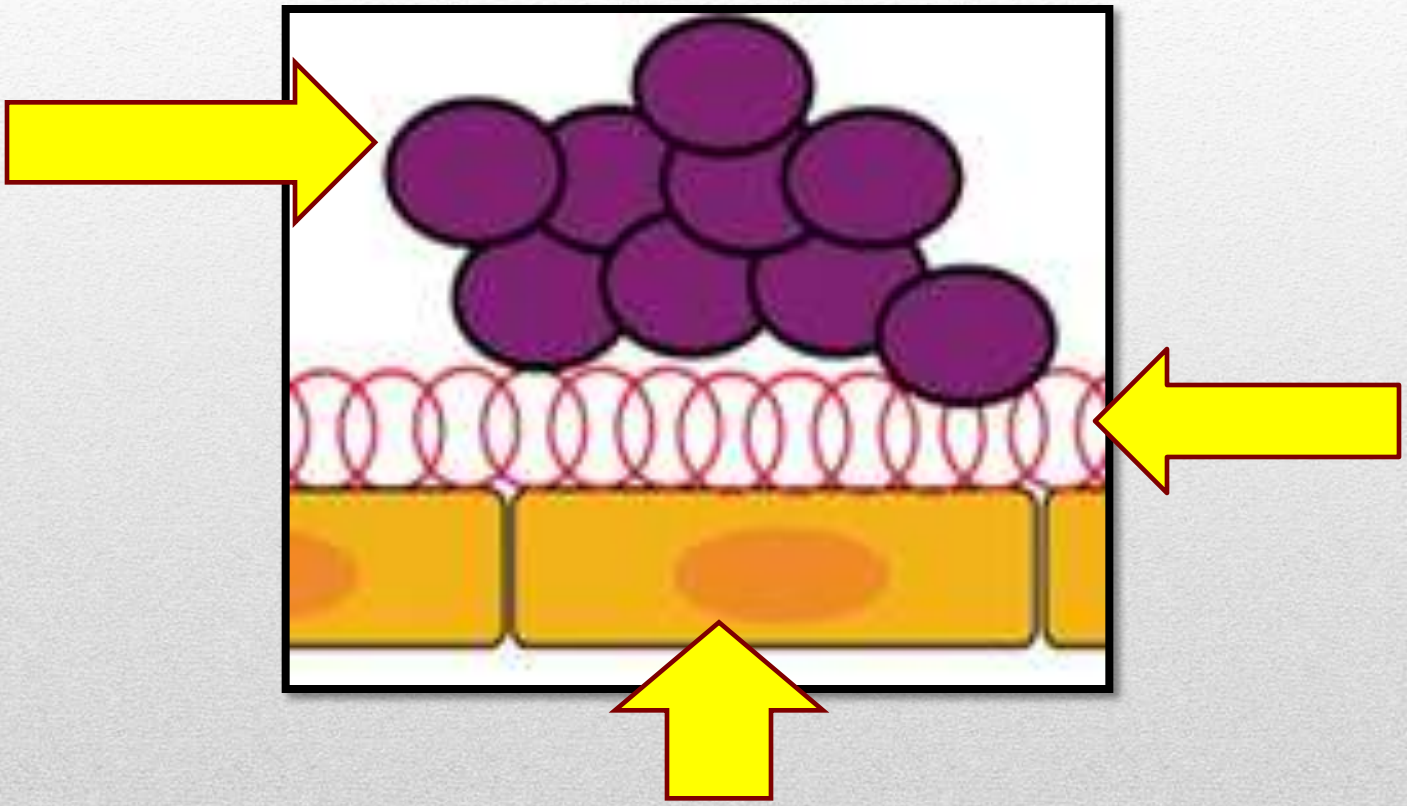
are microvascular occlusive disorders characterized by

- (1)Systemic and or intrarenal aggregation of platelets,
- (2)thrombocytopenia
- (3)mechanical injury to erythrocytes

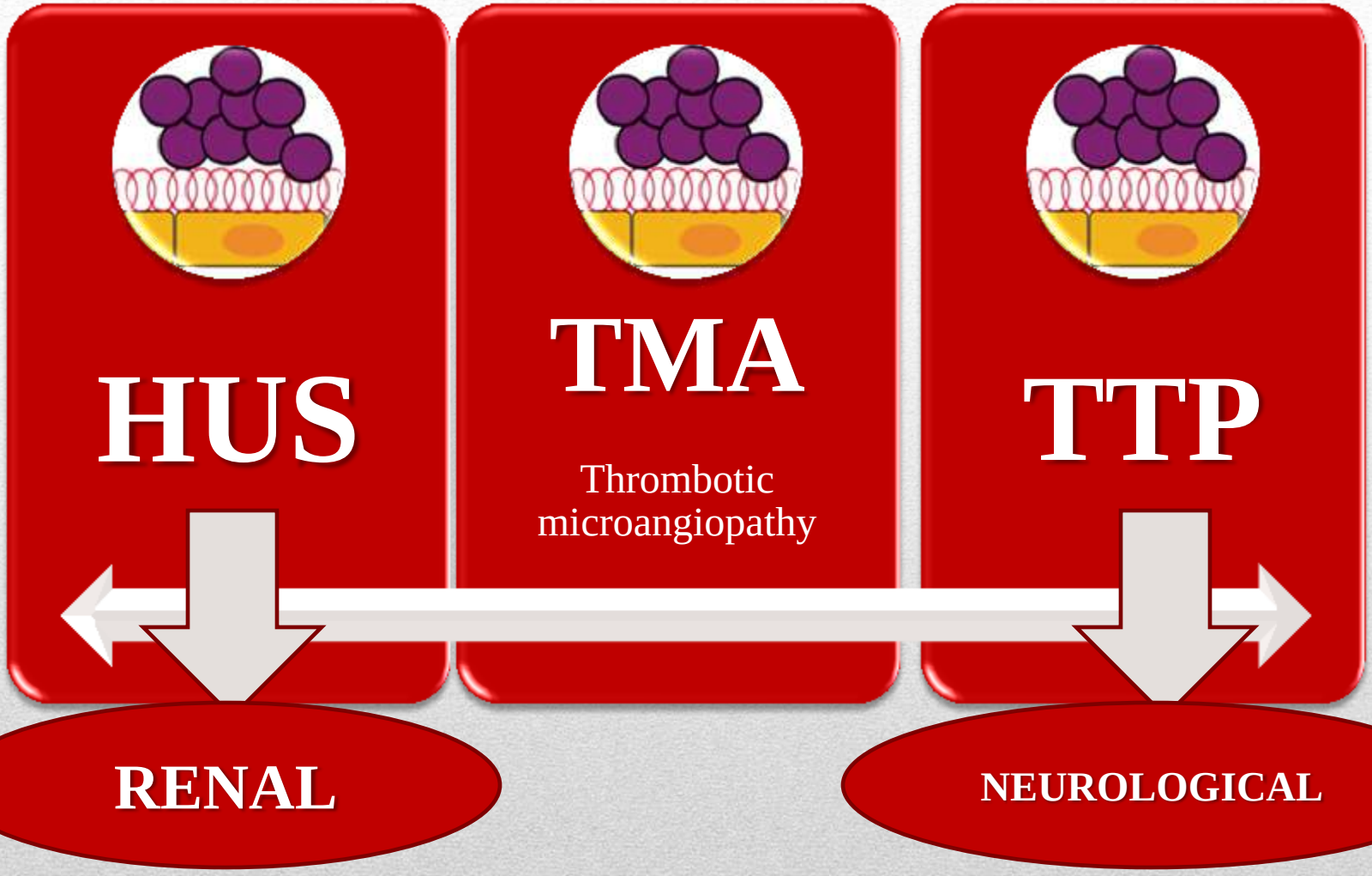
Thrombotic Microangiopathy

THE CRIMINALS IN THE DISEASE

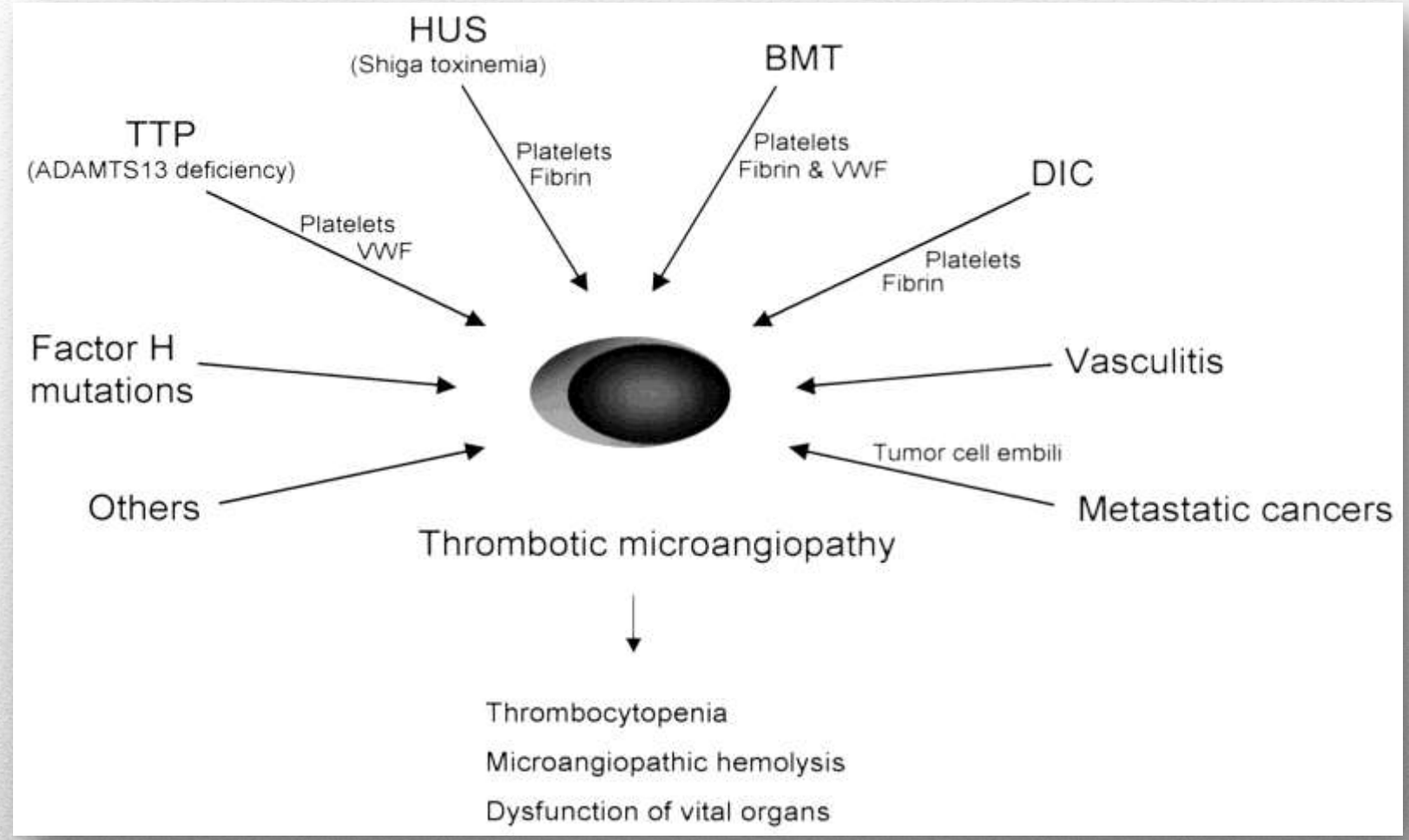
ALL ARE PARTNERS



Thrombotic Microangiopathy



Thrombotic Microangiopathy



Tsai H JASN 2003;14:1072-1081

Thrombotic Microangiopathy

Multiorgan failure

- Hypotension
- Impaired renal perfusion
- Inflammatory mediators:
- Nephrotoxic agents

Abdominal Compartment Syndrome

- ↑intra-abdominal pressures (>20 mm Hg):
  - Trauma.
  - After abdominal surgery
  - Massive fluid resuscitation

Pregnancy related AKI

- Hyperemesis graviderum
- Severe hge during delivery
- Sepsis
- PET & HELLP syndrome
- NSAIDs

Systemic vasculitis	Anti-GBM disease (Goodpasture's) ANCA associated • Wegener's granulomatosis • Microscopic polyarteritis • Churg-Strauss syndrome • Drugs (penicillamine, hydralazine, propylthiouracil) Immune complex disease • Lupus erythematosus • Henoch-Schönlein purpura • Mixed cryoglobulinemia • Rheumatoid vasculitis
Infection	Severe bacterial pneumonia; postinfectious glomerulonephritis; *Legionella;* hantavirus; opportunistic infection in immunocompromised patients; infective endocarditis
Pulmonary edema and AKI	Volume overload; severe left ventricular failure
Multiorgan failure	Acute respiratory distress syndrome and AKI
Other	Paraquat poisoning; renal vein or IVC thrombosis with pulmonary emboli

Pulmonary-Renal Syndromes

Prerenal uremia	Diuretic use, gastrointestinal loss, peritoneal aspiration, hypoalbuminemia
Hepatorenal syndrome	
Acute tubular necrosis	Hyperbilirubinemia, sepsis, toxic shock syndrome
Drugs	Acetaminophen (paracetamol), NSAIDs, tetracycline, rifampicin, isoniazid, anesthetic agents, sulfonamides, allopurinol, methotrexate
Infections	Hepatitis C and cryoglobulinemia, hepatitis B and polyarteritis nodosa, leptospirosis, hantavirus, Epstein-Barr virus, gram-negative sepsis, spontaneous bacterial peritonitis
Other	Papillary necrosis and obstruction, inhalation of chlorinated hydrocarbons, mushroom poisoning (*Amanita phalloides*)

AKI in liver diseases

Prerenal	Nausea and vomiting, hypercalcemia, cardiomyopathy secondary to chemotherapy
Vascular	Thrombotic microangiopathy (adenocarcinoma of stomach, pancreas, prostate; radiation nephropathy), renal vein thrombosis secondary to hypercoagulability, disseminated intravascular coagulation (acute promyelocytic leukemia)
Glomerular	Rapidly progressive glomerulonephritis
Acute tubular necrosis	Sepsis and antibiotic nephrotoxicity, hypercalcemia
Malignant infiltration	Lymphoma, acute lymphoblastic leukemia
Intraluminal obstruction	Tumor lysis syndrome, cast nephropathy
Postrenal obstruction	Transitional cell carcinoma of the ureters/bladder, extrinsic ureteral compression (tumor, nodes, retroperitoneal fibrosis)
Chemotherapeutic agents	
Tubular toxicity	Cisplatin, ifosfamide, plicamycin (mithramycin); 5-fluorouracil, thioguanine (6-thioguanine), cytarabine
Thrombotic microangiopathy	Mitomycin C, bleomycin, cisplatin, calcineurin inhibitors
Other mechanisms	Capillary leak syndrome (IL-2 therapy), acute interstitial nephritis (interferon-α), intraluminal obstruction (methotrexate)

AKI with cancer

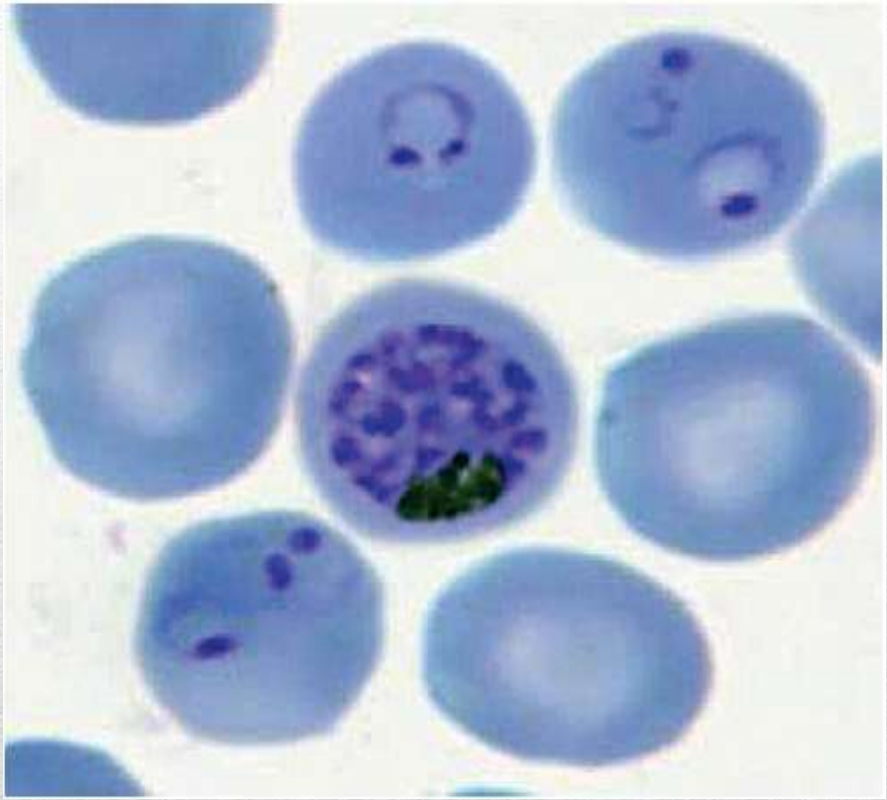
Russell's Viper Snake

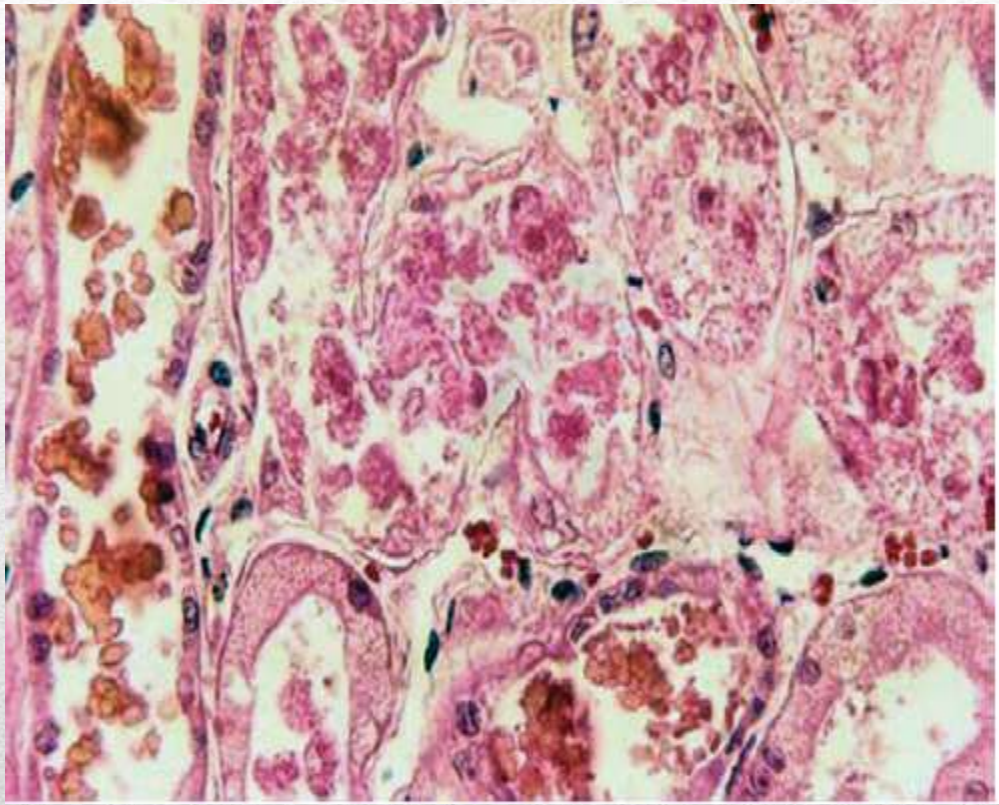
AKI in tropics

Lonomia obliqua caterpillars

Loxosceles spider

AKI in tropics





AKI in tropics

Thank You